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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/528,031 | 03/17/2000 | Andrew Shyjan | MNI-056CPCN | 3941 |

959 7590 01/02/2002

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

| EXAMINER |
|---|
| BRUMBACK, BRENDA G |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 12 |

DATE MAILED: 01/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/528,031 | Applicant(s) ANDREW SHYJAN | |
|---|---|---|---|
| | Examiner Brenda G. Brumback | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *106-108 and 115-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-108 and 115-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restriction*

1. Applicant's election with traverse of Group X in Paper No. 10 is acknowledged. The traversal is on the ground(s) that claim 109 should have been included in Group X. Although applicant's argument is persuasive, as claim 109 was inadvertently left out of Group X, the argument is now moot, as claim 109 has been canceled.

2. Claims 48, 51, 76, 77, 80-105, and 109-114 were canceled. Claims 106-108 were amended. New claims 115-134 were added. Claims 106-108 and 115-134 are pending and under examination.

### *Priority*

3. The current status of the parent nonprovisional applications in the first sentence of the specification should be updated to include the patent numbers.

### *Information Disclosure Statement*

4. The Information Disclosure Statement filed 11/05/2001 is acknowledged. A signed copy is attached hereto.

***Specification***

5. The specification is objected to for the following informality. The Brief Description of the Drawings should be amended to reflect all of the drawings by figure number, *i.e.*, "Figure 1" should be amended to "Figures 1A-1G", etc.

***Claim Objections***

6. Claim 126 is a duplicate of claim 125. Applicant is advised that should claim 125 be found allowable, claim 126 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

***Claim Rejections - 35 USC § 112***

7. Claims 106-108 and 115-134 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of identifying a modulator of MRP-β. The abbreviation MRP-β is not an art recognized term. Thus, it would appear that the abbreviation is applicant's. While applicant may be his or her own lexicographer, a term in a claim must be clearly defined in applicant's disclosure. The specification discloses MRP-β as a "hitherto-

unknown multidrug-resistance associated polypeptide" (page 6, lines 1-2). The specification discloses two preferred embodiments of the polypeptides (page 7), but doesn't define the metes and bounds of other polypeptides which are encompassed within the claimed invention. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

The claims recite that a detectable fluctuation in the level of MRP-β expression, export or sequestration of a substrate, or cell survival indicates that a candidate is an MRP-β modulator; however, the claims fails to disclose what is to be measured in order to determine that a fluctuation has occurred. If the claims are intended to recite a detectable fluctuation in the level in the presence of the candidate compared to the level in the absence of the candidate, then the claims should be amended to so indicate.

The claims recite a "substrate" transported by MRP-β. The specification discloses a "substrate (e.g., a cytotoxin)" at page 21, line 8. It is unclear from the disclosure whether the claimed substrate is equivalent to a cytotoxin or whether a cytotoxin is one species of the claimed genus of substrates. Thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claims 115 and 115 recite "the nucleic acid molecule of SEQ ID NO:2". The sequence disclosure indicates that SEQ ID NO:2 is an amino acid sequence, not a nucleic acid sequence. Thus, the claim is indefinite, as it is unclear to what sequence the claim is drawn. Additionally, claims 115 and 116 recite species of nucleic acid molecules that hybridize under stringent

conditions with the nucleic acid molecule of SEQ ID NO:2. The specification fails to teach the metes and bounds of "stringent conditions". For this reason also, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claims 115-116 recite a polypeptide comprising an amino acid sequence sharing at least 75% sequence identity with the amino acid sequence of SEQ ID NO:2 or encoded by a nucleic acid molecule sharing at least 75% identity with the nucleic acid molecule of SEQ ID NO:1 (SEQ ID NO:1 is assumed to be the intended sequence of the nucleotide, as SEQ ID NO:2 is an amino acid sequence). It is unclear if the claimed polypeptides and nucleic acids share at least 75% overall sequence identity with the recited sequences or whether polypeptides and nucleotides which share at least 75% identity with some portion of the recited sequences are also encompassed. Absent this disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claims 117-124, 129, and 132-133 are indefinite as lacking sufficient clear antecedent basis. The claims recite the limitation "the assay of any one of claims 106-108". Although each of claims 106-108 recite an "assaying" step in the claimed method, the dependent claims refer back to steps other than the "assaying" step; thus, the dependent claims lack sufficient antecedent basis. It is suggested that the term "method" be substituted for "assay" in the claims.

Claim 132 recites a candidate modulator selected from a genus; however, the metes and bounds of the species within the genus are not defined. There is no disclosure in the specification of what is encompassed within "a natural metabolite", "a synthetic chemical", "a

synthetic metabolite", etc. Absent such disclosure, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

The term "small" in claim 133 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 134 recites measuring substances from "an intracellular milieu". The specification fails to disclose what substances are encompassed within such an intracellular milieu; thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

cl 107-108, 115, 117-118, 120-124, 129, 131, 132-133, 136

8. Claims 1-15-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

*Vas-Cath Inc. V. Mahurka*, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117). Although indefinite for the reasons outlined *supra*, a review of the language of the claims indicates that these claims are drawn to a genus, most likely a genus of polypeptides comprising any and all polypeptides sharing at least 75% identity with the amino acid sequence of SEQ ID NO:2, polypeptides encoded by nucleic acid molecules sharing at least 75% sequence identity with SEQ ID NO:1, and polypeptides encoded by nucleic acid molecules that hybridize under stringent conditions with the nucleic acid molecule of SEQ ID NO:1.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such

as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* a polypeptide encoded by a nucleic acid molecule represented by the full length sequence of SEQ ID NO:1 and having the full length amino acid sequence set forth in SEQ ID NO:2. The disclosure of a single may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claims encompass numerous species that are not further described, *i.e.*, polypeptides sharing at least 75% identity with the amino acid sequence of SEQ ID NO:2, polypeptides encoded by nucleic acid molecules sharing at least 75% sequence identity with SEQ ID NO:1, and polypeptides encoded by nucleic acid molecules that hybridize under stringent conditions with the nucleic acid molecule of SEQ ID NO:1. There is substantial variability among the species.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116) because the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides and nucleic acids.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

8. Claim 115 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Because claim 115 specifically requires the use of the plasmid deposited as ATCC Deposit No. 94809, a suitable deposit of the plasmid for patent purposes is required or evidence must be provided that the plasmid is well known and readily available to the public. It is not clear from the disclosure that deposits of the plasmid ATCC Deposit No. 94809 meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

9. Claims 106-108 and 115-134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for identifying drugs which inhibit MRP-β by testing for MRP-β expression, for cell survival, or for sequestration of a cytotoxin, does not reasonably provide enablement for identifying stimulatory modulators of MRP-β, does not reasonably provide enablement for the scope of the modulators of claim 132, and does not reasonably provide enablement for identifying modulators by testing for sequestration of substrates other than cytotoxins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni,

195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the full scope of the claimed invention for the following reasons:

*The nature of the invention:* Although indefinite for the reasons set forth *supra*, for purposes of examination herein, the claimed invention has been interpreted as drawn to a method of identifying either a stimulatory or an inhibitory modulator of MRP-β expression in a cell comprising contacting the cell with a candidate modulator and testing for the level of MRP-β expression; or contacting a cell with candidate modulator and a substrate transported by MRP-β and testing for fluctuation in export or sequestration of the substrate; or contacting the cell with a cytotoxin and the candidate modulator of MRP-β and testing for cell survival. Dependent claim 132 recites the candidate modulator as selected from a genus of modulator species comprising "a natural metabolite", "a synthetic chemical", "a synthetic metabolite", "a naturally sourced chemical", and " a naturally sourced secretion product", among others.

*The state of the prior art and the predictability or lack thereof in the art:* The art teaches that certain drugs, such as verapamil (a calcium channel blocker) (see Solary et al. Leukemia 5/7:592-597, July 1991, the abstract) and safingol (a protein kinase) (see Sachs et al., The Journal of Biological Chemistry 270/44:26639-26648, 1995), inhibit multidrug resistance. Sachs et al.

teach that modulators of multidrug resistance are inhibitors which interfere with specific binding of drugs to the P-glycoprotein in membranes derived from the cell membranes of multidrug-resistant cells (see page 26639, column 2, first two sentences). Chao (Environmental Toxicology and Pharmacology 1:63-72, 1996) teaches that multidrug resistant cells show decreased intracellular accumulation of cytotoxic agents (see page 63, column 2 in its entirety) and that drugs which modulate multidrug resistance enhance intracellular drug accumulation, and that drug efflux can be measured in order to identify an inhibitor of multidrug resistance (see page 67, the paragraph bridging columns 1 and 2). The art does not teach that sequestration of substrates other than cytotoxins can be measured for identifying modulators of multidrug resistance. The art does not teach modulators of multidrug resistance as corresponding in scope with "natural metabolites", "synthetic chemicals", "synthetic metabolites", "naturally sourced chemicals", or " naturally sourced secretion products" and the other embodiments recited in the claims. The art does not teach stimulatory modulators of multidrug resistance.

*The amount of direction or guidance present and the presence or absence of working examples:* Given the teachings of unpredictability found in the art, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to practice the invention commensurate in scope with the claims. These teachings are absent. While there are some general teachings found in the disclosure (see pages 50-55) regarding the state of the art as to cellular susceptibility testing for cytotoxic drugs and published guidelines for discovery of new drugs (see especially page 51, lines 10-13), there are no specific teachings of how to identify

modulators of MRP-β. There is no guidance as to how to select appropriate candidate modulators for testing. There are no working examples disclosing identification of any heretofore unknown modulators of MRP-β.

*The breadth of the claims and the quantity of experimentation needed:* Because the claims encompass identification of heretofore unknown modulators of MRP-β, encompass assaying for fluctuations of substrates other than known chemotherapeutic cytotoxic drugs, and encompass identification of heretofore unknown simulators of multidrug resistance and in light of the teachings of the unpredictability found in the art and the lack of sufficient teachings in applicant's disclosure to overcome those teachings, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

### *Claim Rejections - 35 USC § 102*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

a. Claims 108, 117, 118, 120, 121-123, 129, and 131-133 are rejected under 35 U.S.C. 102(b) as being anticipated by Solary et al.

Although indefinite for the reasons set forth *supra*, the claimed invention has been interpreted as drawn to a method of identifying a modulator of MRP-β comprising contacting a MRP-β expressing human host cell with a cytotoxin and a candidate modulator of MRP-β and assaying survival of the cell, wherein a detectable fluctuation in cell survival in the presence of the candidate modulator compared to that in the absence of the candidate modulator indicates that the candidate is a modulator of MRP-β.

Solary et al. teach identification of a modulator (inhibitor) of multidrug resistance comprising contacting a multidrug resistant human host cell with the cytotoxic drug, doxorubicin, and a modulator of multidrug resistance, verapamil, and assaying survival of the cell with and without verapamil (see the document in its entirety and especially the abstract). Although Solary et al. teach that the mechanism of the multidrug resistance is the P-glycoprotein, Solary et al. anticipate the claimed invention for two reasons. Firstly, as set forth previously, applicant's disclosure teaches MRP-β as a "multidrug resistance associated polypeptide". The P-glycoprotein is taught in the art to be a multidrug resistance associated polypeptide. Secondly, if the method of the prior art inherently performs the function of the claimed invention, then the method anticipates the claimed invention. The method steps of the method of Solary et al. would inherently identify a modulator of MRP-β.

b. Claims 106-108, 117, 118, 120, 121-123, 125-127, and 129-134 are rejected under 35 U.S.C. 102(b) as being anticipated by Chao.

The claimed invention has been interpreted as drawn to a method of identifying a modulator of MRP-β by contacting a MRP-β expressing human host cell with a candidate modulator and assaying the level of expression of MRP-β polynucleotide or polypeptide in the presence and absence of the candidate modulator; by contacting a MRP-β expressing human host cell with a candidate modulator and a cytotoxin substrate and assaying export or sequestration of the cytotoxin, wherein a detectable fluctuation in either cell survival or cytotoxin sequestration identifies the candidate as a modulator of MRP-β; or by contacting an MRP-β expressing human host cell with a candidate modulator and assaying cell survival, wherein a detectable fluctuation in the presence and absence of the candidate identifies the candidate as an MRP-β modulator.

Chao teaches a method of identifying verapamil as a modulator of multidrug resistance by contacting multidrug resistant B lymphoma cells with the cytotoxic drug vincristine and verapamil and assaying the level of intracellular drug accumulation (see page 67, the paragraph bridging columns 1 and 2). Chao teach that multidrug resistance can also be measured by measuring expression of the *mdr1* gene by PCR, by measuring cellular levels of P-glycoprotein, and by assaying for cell survival (see the document in its entirety and especially the abstract). Although Chao does not teach the mechanism of multidrug resistance as MRP-β, Chao anticipates the claimed method for the same reasons as those outlined above for Solary et al.

c. Claims 106-108, 117, 118, and 120-134 are rejected under 35 U.S.C. 102(b) as being anticipated by Sachs et al.

The claimed invention is as described above with the further limitation of the human host cell as MCF-7.

Sachs et al. teach a method of identifying safingol as a modulator of multidrug resistance by contacting MCF-7 cells with the cytotoxic drug safingol and verapamil and assaying the level of intracellular drug accumulation (see page 26640, column 2, third full paragraph). Sachs et al. teach that multidrug resistance can also be measured by measuring expression of the *mdr1* gene, by measuring cellular levels of P-glycoprotein, and by assaying for cell survival (see page 26639, the abstract and first paragraph, and page 26640, the paragraph bridging columns 1 and 2, through page 26640, first full paragraph). Although Sachs et al. do not teach the mechanism of multidrug resistance as MRP-β, Sachs et al. also anticipate the claimed method for the same reasons as those outlined above for Solary et al.

***Claim Rejections - 35 USC § 103***

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 106-108, 115-118, 120-121 and 123-134 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sachs et al. in view of Kool et al. (See Result # 4 in the

Sequence Search conducted 11/09/2001, Accession No. U83661, GemEmbl Database, submitted January 03, 1997).

The claimed invention is as previously described with the additional limitation that the MRP-β polypeptide is selected from a polypeptide comprising the amino acid sequence of SEQ ID NO:2, a polypeptide sharing at least 75% sequence identity with SEQ ID NO:2, a polypeptide encoded by the nucleic acid of SEQ ID NO:1, a polypeptide encoded by a nucleic acid sharing at least 75% identity with the nucleic acid of SEQ ID NO:2, or a polypeptide encoded by a nucleic acid that hybridizes under stringent conditions with the nucleic acid of SEQ ID NO:1.

As set forth *supra,* Sachs et al. teach a method of identifying safingol as a modulator of multidrug resistance by contacting MCF-7 cells with the cytotoxic drug safingol and verapamil and assaying the level of intracellular drug accumulation. Sachs et al. teach that multidrug resistance can also be measured by measuring expression of the *mdr1* gene, by measuring cellular levels of P-glycoprotein, and by assaying for cell survival. Sachs et al. do not teach the mechanism of multidrug resistance as a multidrug resistance associated polypeptide selected from a polypeptide comprising the amino acid sequence of SEQ ID NO:2, a polypeptide sharing at least 75% sequence identity with SEQ ID NO;2, a polypeptide encoded by the nucleic acid of SEQ ID NO:1, a polypeptide encoded by a nucleic acid sharing at least 75% identity with the nucleic acid of SEQ ID NO:2, or a polypeptide encoded by a nucleic acid that hybridizes under stringent conditions with the nucleic acid of SEQ ID NO:1.

Kool et al. teach homologues of the multidrug resistance associated protein gene *mrp1* which have 98.8% identity and 99.9% local similarity with the polynucleotide of SEQ ID NO:1.

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have tested for modulators of multidrug resistance using the multidrug resistance associated polypeptide disclosed by Kool et al. in order to be able to identify additional potentially useful chemotherapeutics.

b. Claims 119 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of Solary et al., Chao, or Sachs et al. in view of Raymond et al. (Molecular and Cellular Biology 14/1:277-286, 1994).

The claimed invention is as described *supra*, with the additional limitation that the MRP-β be vector derived. Any of Solary et al., Chao, or Sachs teach multidrug resistant cells expressing a multidrug resistance associated polypeptide (the P-glycoprotein). None of Solary et al., Chao, or Sachs teach the polypeptide as vector-derived.

Raymond et al. teach introduction of the *mdr3* gene into a *Saccharomyces cerevisiae* host cell, which results in conference of drug resistance to the host cell (see the title and abstract).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have introduced a multidrug resistance gene into a host cell for the purpose of testing for modulators of multidrug resistance, as a means of identifying agents which mediate multidrug resistance through a well-defined mechanism.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
December 13, 2001

Brenda Brumback
Brenda Brumback,
Patent Examiner